

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

1-37. Cancelled.

38. (currently amended) ~~a~~ A method for modifying glucose metabolism in a glucose intolerant animal, comprising administering to the animal, in a single daily oral dosage, a composition including one or more protease inhibitors which inhibit DPIV-mediated proteolysis with a K_i ~~in the nanomolar or less range~~ of less than about 10 nM.

39. (currently amended) A method for modifying glucose metabolism in a glucose intolerant animal, comprising administering to the animal, in a single daily oral dosage, a composition including one or more protease inhibitors which inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) with a K_i of less than about 10 nM ~~in the nanomolar or less range~~.

40. (currently amended) A method for modifying metabolism of a peptide hormone in a glucose intolerant animal, comprising administering to the animal a composition, in a single daily oral dosage, including one or more inhibitors of dipeptidylpeptidase IV (DPIV), wherein the inhibitor inhibits DPIV with a K_i of less than about 10 nM ~~in the nanomolar or less range~~, in an amount sufficient to increase the plasma half-life of the peptide hormone, which peptide hormone is selected from glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y.

41. (original) A method for modifying glucose metabolism of a glucose intolerant animal, comprising administering to the animal a composition including a boronyl

peptidomimetic inhibitor of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

42. (original) The method of claim 41 wherein, the glucose intolerance in the animal is a result of a deletion or disruption of the gene encoding for a glucagon type peptide 1 (GLP-1) receptor.

43. (Cancelled)

44, 45. (Cancelled)

46. (original) The method of claim 38, 39, 40 or 41, wherein administering the inhibitor reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

47. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

48. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor has an EC_{50} for inhibition of glucose tolerance in the nanomolar or less range.

49. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor has an EC_{50} for immunosuppression in the μM or greater range.

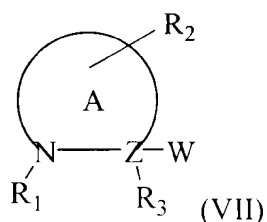
50. (original) The method of any of claim 38, 39, 40 or 41, wherein the inhibitor has a K_i for DPIV inhibition of 0.5 nM or less.

51. (original) The method of claim 38, 39, or 40, wherein the inhibitor is peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

52. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor has a molecular weight less than 7500 amu.

53. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor is administered orally.

54. (currently amended) ~~the~~ The method of claim 38, 39, 40 or 41, wherein the inhibitor is represented by the general Formula VII:

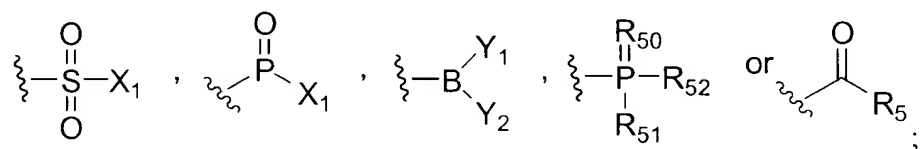


wherein,

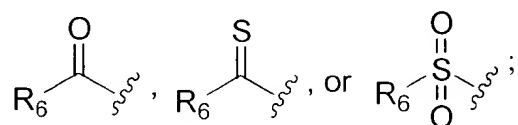
A represents a 4-8 membered heterocycle including a N and a C α carbon;

Z represents C or N;

W represents -CH=NR₅,



R₁ represents a C-terminally linked amino acid residue or a amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group,



R₂ is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -(CH₂)_m-R₇, -(CH₂)_m-OH, -(CH₂)_m-

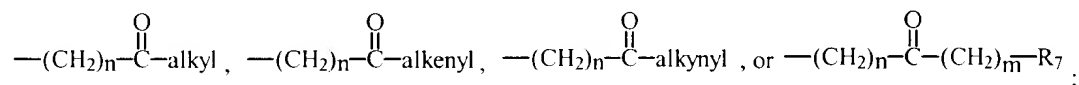
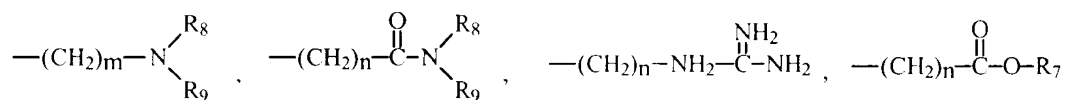
O-lower alkyl, $-(CH_2)_m$ -O-lower alkenyl, $-(CH_2)_n$ -O- $(CH_2)_m$ -R₇, $-(CH_2)_m$ -SH, $-(CH_2)_m$ -S-lower alkyl, $-(CH_2)_m$ -S-lower alkenyl, or $-(CH_2)_n$ -S- $(CH_2)_m$ -R₇;

if Z is N, R₃ represents a hydrogen;

if Z is C, R₃ represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m$ -R₇, $-(CH_2)_m$ -OH, $-(CH_2)_m$ -O-lower alkyl, $-(CH_2)_m$ -O-lower alkenyl, $-(CH_2)_n$ -O- $(CH_2)_m$ -R₇, $-(CH_2)_m$ -SH, $-(CH_2)_m$ -S-lower alkyl, $-(CH_2)_m$ -S-lower alkenyl, or $-(CH_2)_n$ -S- $(CH_2)_m$ -R₇;

R₅ represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m$ -R₇, $-(CH_2)_n$ -OH, $-(CH_2)_n$ -O-alkyl, $-(CH_2)_n$ -O-alkenyl, $-(CH_2)_n$ -O-alkynyl, $-(CH_2)_n$ -O- $(CH_2)_m$ -R₇, $-(CH_2)_n$ -SH, $-(CH_2)_n$ -S-alkyl, $-(CH_2)_n$ -S-alkenyl, $-(CH_2)_n$ -S-alkynyl, $-(CH_2)_n$ -S- $(CH_2)_m$ -R₇, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'$;

R₆ represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m$ -R₇, $-(CH_2)_m$ -OH, $-(CH_2)_m$ -O-alkyl, $-(CH_2)_m$ -O-alkenyl, $-(CH_2)_m$ -O-alkynyl, $-(CH_2)_m$ -O- $(CH_2)_m$ -R₇, $-(CH_2)_m$ -SH, $-(CH_2)_m$ -S-alkyl, $-(CH_2)_m$ -S-alkenyl, $-(CH_2)_m$ -S-alkynyl, $-(CH_2)_m$ -S- $(CH_2)_m$ -R₇,



R₇ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'₇ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R₈ and R₉ each independently represent hydrogen, alkyl, alkenyl, -(CH₂)_m-R₇, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-(CH₂)_m-R₇,

or R₈ and R₉ taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R₅₀ represents O or S;

R₅₁ represents N₃, SH, NH₂, NO₂ or OR'₇;

R₅₂ represents hydrogen, a lower alkyl, an amine, OR'₇, or a pharmaceutically acceptable salt, or R₅₁ and R₅₂ taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

Y₁ and Y₂ can independently or together be OH or an alkoxy, or taken together Y₁ and Y₂ are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

X₁ represents a halogen;

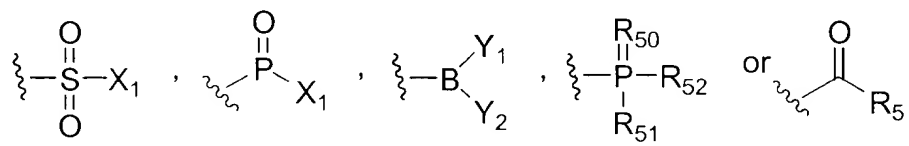
X₂ and X₃ each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

55. (original) The method of claim 54, wherein

W represents -CH=NR₅,



R₅ represents a hydrogen, an alkyl, an alkenyl, an alkynyl, -C(X₁)(X₂)X₃, -(CH₂)_m-R₇, -(CH₂)_n-OH, -(CH₂)_n-O-alkyl, -(CH₂)_n-O-alkenyl, -(CH₂)_n-O-alkynyl, -(CH₂)_n-O-(CH₂)_m-R₇, -(CH₂)_n-SH, -(CH₂)_n-S-alkyl, -(CH₂)_n-S-alkenyl, -(CH₂)_n-S-alkynyl, -(CH₂)_n-S-(CH₂)_m-R₇, -C(O)C(O)NH₂, or -C(O)C(O)OR'₇;

R₇ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'₇ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

Y₁ and Y₂ can independently or together be hydroxyl, or taken together Y₁ and Y₂ are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

R₅₀ represents O or S;

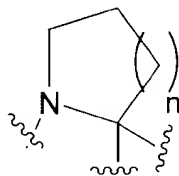
R₅₁ represents N₃, SH, NH₂, NO₂ or OR'₇;

R₅₂ represents hydrogen, a lower alkyl, an amine, OR'₇, or a pharmaceutically acceptable salt, or R₅₁ and R₅₂ taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X₁ represents a halogen; and

X₂ and X₃ each represent a hydrogen or a halogen.

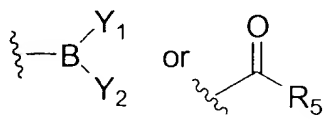
56. (original) The method of claim 54, wherein the ring A is represented by the formula



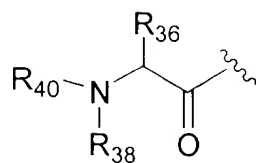
wherein,

n is an integer of 1 or 2.

57. (previously presented) The method of claim 54, wherein W represents



58. (original) The method of claim 54, wherein R_1 represents



R_{36} represents a small hydrophobic group and R_{38} is hydrogen, or, R_{36} and R_{38} together form a 4-7 membered heterocycle including the N and the $C\alpha$ carbon, as defined for A above; and

R_{40} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

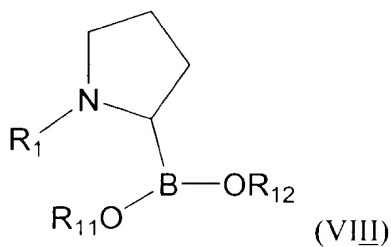
59. (original) The method of claim 54, wherein R_2 is absent, or represents a small hydrophobic group.

60. (original) The method of claim 54, wherein R_3 is a hydrogen, or a small hydrophobic group.

61. (original) The method of claim 54, wherein R_5 is a hydrogen, or a halogenated lower alkyl.

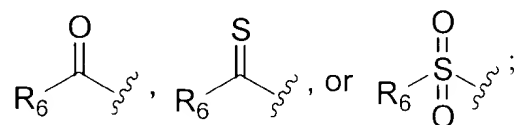
62. (original) The method of claim 54, wherein X_1 is a fluorine, and X_2 and X_3 , if halogens, are fluorine.

63. (original) The method of claim 54, wherein the inhibitor is represented by the general Formula (VIII):

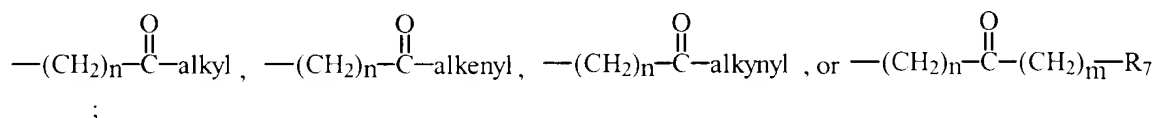
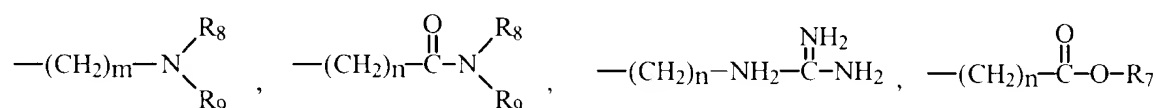


wherein,

R₁ represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog,



R₆ represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -(CH₂)_m-R₇, -(CH₂)_m-OH, -(CH₂)_m-O-alkyl, -(CH₂)_m-O-alkenyl, -(CH₂)_m-O-alkynyl, -(CH₂)_m-O-(CH₂)_m-R₇, -(CH₂)_m-SH, -(CH₂)_m-S-alkyl, -(CH₂)_m-S-alkenyl, -(CH₂)_m-S-alkynyl, -(CH₂)_m-S-(CH₂)_m-R₇,



R₇ represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

R₈ and R₉ each independently represent hydrogen, alkyl, alkenyl, -(CH₂)_m-R₇, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-(CH₂)_m-R₇,

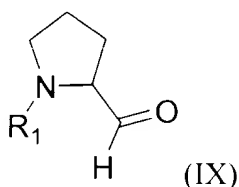
or R₈ and R₉ taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R₁₁ and R₁₂ each independently represent hydrogen, an alkyl, or a pharmaceutically acceptable salt, or R₁₁ and R₁₂ taken together with the O-B-O atoms to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

m is zero or an integer in the range of 1 to 8; and

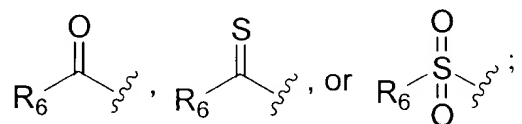
n is an integer in the range of 1 to 8.

64. (previously presented) The method of claim 54, wherein the inhibitor is represented by the general Formula IX:

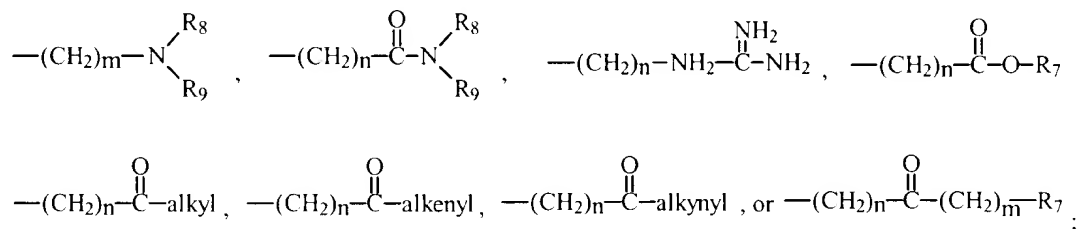


wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog,



R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O\text{-alkyl}$, $-(CH_2)_m-O\text{-alkenyl}$, $-(CH_2)_m-O\text{-alkynyl}$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S\text{-alkyl}$, $-(CH_2)_m-S\text{-alkenyl}$, $-(CH_2)_m-S\text{-alkynyl}$, $-(CH_2)_m-S-(CH_2)_m-R_7$,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

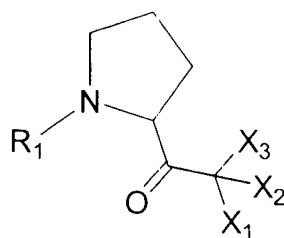
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, $-C(=O)\text{-alkyl}$, $-C(=O)\text{-alkenyl}$, $-C(=O)\text{-alkynyl}$, or $-C(=O)\text{-(CH}_2)_m-R_7$,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

m is zero or an integer in the range of 1 to 8; and

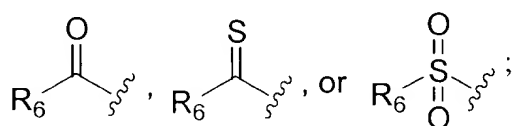
n is an integer in the range of 1 to 8.

65. (previously presented) The method of claim 54, wherein the inhibitor is represented by the general formula:

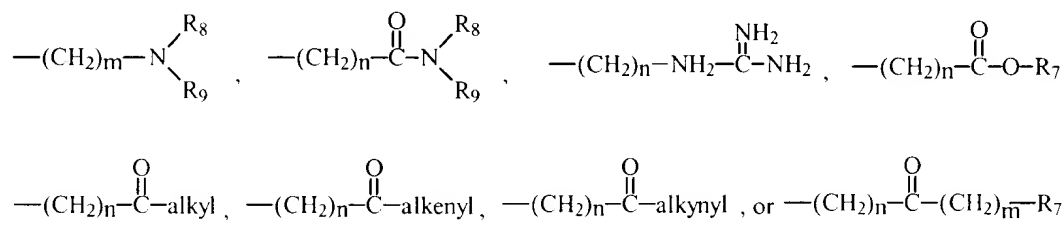


wherein,

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide, or peptide analog,



R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-alkyl$, $-(CH_2)_m-O-alkenyl$, $-(CH_2)_m-O-alkynyl$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-alkyl$, $-(CH_2)_m-S-alkenyl$, $-(CH_2)_m-S-alkynyl$, $-(CH_2)_m-S-(CH_2)_m-R_7$,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, $-C(=O)-alkyl$, $-C(=O)-alkenyl$, $-C(=O)-alkynyl$, $-C(=O)-(CH_2)_m-R_7$, or

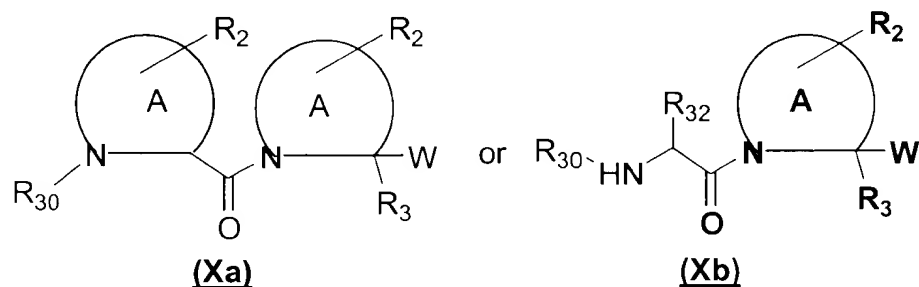
R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

X_1 , X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

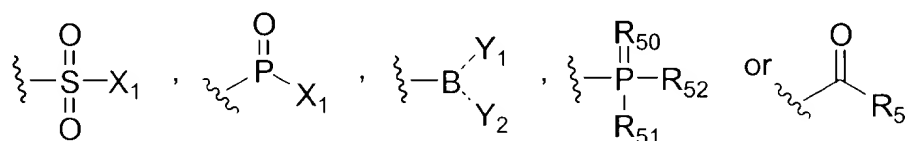
66. (currently amended) the method of claim 54, wherein the inhibitor is represented by the general Formula Xa or Xb:



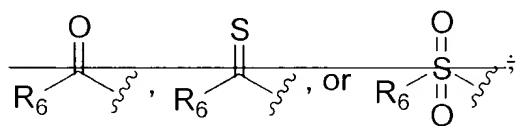
wherein,

A represents a 4-8 membered heterocycle including a N and a C α carbon;

W represents $-\text{CN}$, $-\text{CH}=\text{NR}_5$,



~~R₁ represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group,~~

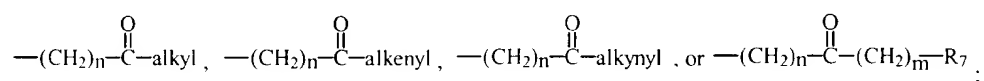
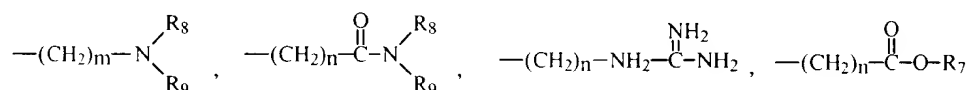


R₂ is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(\text{CH}_2)_m\text{-R}_7$, $-(\text{CH}_2)_m\text{-OH}$, $-(\text{CH}_2)_m\text{-O-lower alkyl}$, $-(\text{CH}_2)_m\text{-O-lower alkenyl}$, $-(\text{CH}_2)_m\text{-O-}(\text{CH}_2)_m\text{-R}_7$, $-(\text{CH}_2)_m\text{-SH}$, $-(\text{CH}_2)_m\text{-S-lower alkyl}$, $-(\text{CH}_2)_m\text{-S-lower alkenyl}$, or $-(\text{CH}_2)_m\text{-S-}(\text{CH}_2)_m\text{-R}_7$.

R₃ represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -lower alkyl, $-(CH_2)_m-O$ -lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -lower alkyl, $-(CH_2)_m-S$ -lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R₅ represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$ -alkyl, $-(CH_2)_n-O$ -alkenyl, $-(CH_2)_n-O$ -alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$ -alkyl, $-(CH_2)_n-S$ -alkenyl, $-(CH_2)_n-S$ -alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

~~R₆ represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -alkyl, $-(CH_2)_m-O$ -alkenyl, $-(CH_2)_m-O$ -alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -alkyl, $-(CH_2)_m-S$ -alkenyl, $-(CH_2)_m-S$ -alkynyl, $-(CH_2)_m-S-(CH_2)_m-R_7$;~~



R₇ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'₇ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

~~R₈ and R₉ each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, $-C(=O)$ -alkyl, $-C(=O)$ -alkenyl, $-C(=O)$ -alkynyl, or $-C(=O)-(CH_2)_m-R_7$;~~

~~or R₈ and R₉ taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;~~

R₃₂ is a small hydrophobic group;

R₃₀ represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group;

R₅₀ represents O or S;

R₅₁ represents N₃, SH, NH₂, NO₂ or OR'₇;

R₅₂ represents hydrogen, a lower alkyl, an amine, OR'₇, or a pharmaceutically acceptable salt, or R₅₁ and R₅₂ taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

Y₁ and Y₂ can independently or together be OH or an alkoxyl, or taken together Y₁ and Y₂ are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

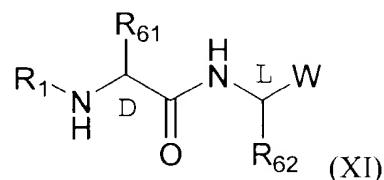
X₁ represents a halogen;

X₂ and X₃ each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

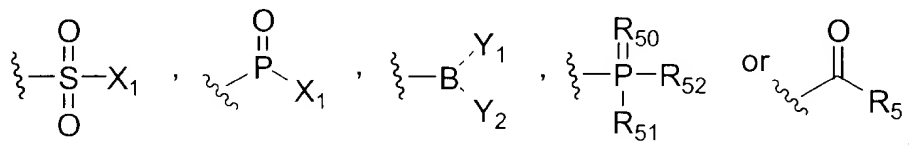
n is an integer in the range of 1 to 8.

67. (previously presented) The method of claim 38, 39, or 40, wherein the inhibitor is represented by the general Formula XI:

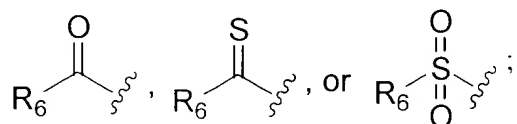


wherein,

W represents a functional group which reacts with an active site residue of the targeted protease selected from -CN, -CH=NR₅,



R₁ represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group, or



R₃ represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -lower alkyl, $-(CH_2)_m-O$ -lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -lower alkyl, $-(CH_2)_m-S$ -lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R₅ represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$ -alkyl, $-(CH_2)_n-O$ -alkenyl, $-(CH_2)_n-O$ -alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$ -alkyl, $-(CH_2)_n-S$ -alkenyl, $-(CH_2)_n-S$ -alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R₆ represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$ -alkyl, $-(CH_2)_m-O$ -alkenyl, $-(CH_2)_m-O$ -alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$ -alkyl, $-(CH_2)_m-S$ -alkenyl, $-(CH_2)_m-S$ -alkynyl, or $-(CH_2)_m-S-(CH_2)_m-R_7$;

R₇ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'₇ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R₆₁ and R₆₂, independently, represent small hydrophobic groups;

Y₁ and Y₂ can independently or together be OH or an alkoxyl, or taken together Y₁ and Y₂ are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

R₅₀ represents O or S;

R₅₁ represents N₃, SH, NH₂, NO₂ or OR'₇;

R₅₂ represents hydrogen, a lower alkyl, an amine, OR'₇, or a pharmaceutically acceptable salt, or R₅₁ and R₅₂ taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X₁ represents a halogen;

X₂ and X₃, independently for each occurrence, represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

68. (New) The method of any of claims 38-40, wherein the total dosage is less than 2000 mg.